Molecular Diagnostics and their Evolving Influence on the Healthcare System

Harry Glorikian, Founder and Managing Partner

Scientia Advisors LLC
55 Cambridge Parkway, 300E
Cambridge, MA 02142
www.scientiaadv.com

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Cambridge, MA
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- WHO WE ARE ENABLES US TO UNDERSTAND OUR CLIENTS’ BUSINESS
- WHO WE ARE ENABLES US TO RAPIDLY IDENTIFY AND DEFINE OUR CLIENT’S PROBLEMS AND GENERATE HYPOTHESES
- WE LEVERAGE OUR DEEP INTERNAL AND EXTERNAL EXPERTISE TO ANALYZE PROBLEMS AND FORMULATE CREATIVE SOLUTIONS
- OUR ROBUST QUANTITATIVE AND QUALITATIVE CAPABILITIES ALLOW US TO GENERATE COMPREHENSIVE STRATEGIC RECOMMENDATIONS

EFFECTIVE STRATEGIC & OPERATIONAL DECISIONS FROM BOARDROOM TO BENCH
Agenda

• The Role of MDx in Personalized Medicine
  » Recent Industry Trends
  » Evolution of Business Models
• Public Policy Considerations
• Future Directions
What is Personalized Medicine (PM)?

Best responders to therapy are identified using Personalized Medicine Tests and then given the Targeted therapy at the right time to maximize efficacy and minimize adverse reaction.
World of Healthcare is Changing - Healthcare stakeholders are increasingly interested in more personalized delivery medicine, creating a great catalyst not just for pharma …

**Regulators**
- Greater integration of Rx and Dx for more efficient and safer clinical trials (e.g. critical path initiative)
- Increased vigilance on drug approvals
- Increased approval of tests that influence safety & efficacy of

**Diagnostic & Pharma Companies**
- Research advances in biomarker discovery and systems biology is translating into more Dx tests
- Enables focused trials – smaller groups for shorter periods with better results
- Dx facilitates better Rx sales by enabling better market penetration and expansion

**Payers**
- Payment for performance
- Payors are pushing for Rx-Dx integration, especially diagnostics that reduce healthcare expenditure e.g. Oncotype Dx

**Patients & Physicians**
- Increasing influence of patient advocacy groups
- Personalized medicine reduces unnecessary therapies, leading to fewer side effects

Source: Scientia Analysis
… but also for hospitals and PBMs such that all the stakeholders are taking initiatives to capitalize on applications of MDx technologies

**HOSPITALS**
- Actively adopting PM measures to obtain better outcomes
- Developing CDSS to control prescription behavior
- Employing whole genome sequencing to direct clinical decisions

**PHARMACY BENEFIT MANAGERS**
- Increased involvement in the personalized medicine revolution
- Establishing themselves as a control point for clinical information
- Will have a significant impact on physician prescription decisions

**LIFE SCIENCE TOOLS COMPANIES**
- Whole genome sequencing - Developing next generation sequencing platforms promise large clinical utility with whole genome sequencing for personalized medicine such as
  - Identifying new biomarkers & genetic targets
  - Simplifying technology for diagnosing genetic biomarkers

Source: Scientia Analysis
Healthcare business models and partnerships are evolving among the major stakeholders as a result of newfound applications of MDx technologies across the healthcare spectrum.
Molecular Diagnostics (MDx) are clinical tests based on measurements of nucleic acids (e.g., DNA or RNA)

MOLECULAR DIAGNOSTICS (MDx)*:
Molecular diagnostics is the detection of DNA/RNA and its variation with the intent to diagnose disease, determine a patient’s susceptibility to disease, evaluate response to therapy or establish the condition’s prognosis

MDx TESTING & INFORMATION ...
- Gene sequencing
- Micorarrays
- Signal amplification
- Strand Displacement Amplification (SDA)
- Transcription Mediated Amplification (TMA)
- pPCR

... PERSONALIZED HEALTHCARE...
- Oncology
- Genetic diseases
- Blood screening
- Infectious diseases
- Other

Sources: Scientia analysis, FDA, CDC; * Includes analyte specific reagents and revenue from CLIA^ certified labs that supply their own IVD product that is an analyte specific reagent or approved by a regulatory body (e.g. Genomic Health)
Diagnostic companies have made significant strides in advancing personalized medicine; now with the cooperation of pharma, we expect rapid growth in tests

**KEY TAKEAWAYS**

- Diagnostics are having a large role in personalized medicine due to its ability to
  - Identify suitable patient subsets for targeted therapies
  - Identify patients who may have significant adverse effects
  - Identify patients who will respond to classes of drugs

- Diagnostics in personalized medicine used to be focused on drugs already on the market such as Amplichip and Verigene CYP2C19, now many diagnostic companies have forged relationships with pharma in hopes of developing companion diagnostic tests for drugs in the pipeline such as DxS’s (Qiagen) collaborations with Boehringer Ingelheim’s (NSCLC) and Pfizer’s (Brain Cancer) drug candidates
As result, unlike in the past, applications of MDx technologies have expanded beyond finding one customized treatment for each patient.

In the past, MDx technologies were mainly targeted towards the final goal of personalized medicine - 1 treatment customized per patient ... … however, now, MDx technologies are being targeted to various different aspects of clinical development to improve R&D & patient care.

**MOLECULAR DIAGNOSTICS TOOLS & TECHNOLOGIES**

Non-exhaustive list of MDx applications for clinical development & patient care

- Acute Care – identifying patient sub-groups
-Whole Genome Sequencing - diagnostic tool for specific patient’s cancer pathway & therapy selection
- Pharma introducing diagnostics earlier in the drug trial process (MetMab + Tarceva)
- Custom Treatment
- 1 Person
- Optimizing drug discovery for a subset of patients
- Chronic Care – Early detection & Prevention
- Rx/Dx Studies with IVD companies (CPT Coding Program)

Source: Scientia Analysis

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Even though advances in MDx has paved the way for personalized medicine, healthcare is still evolving from generalized care to personalized care

PERSONALIZED HEALTHCARE:
Personalized Healthcare is the custom design and implementation of health care for every individual. This would include personalized solutions across the health spectrum, from health & wellness, to chronic disease management, to acute care.

» Personalized Healthcare is a function of:
  1. **Upfront information** that can segment populations by health status into an ever increasing number of sub-categories
  2. **Direction of Therapy**: An increasing number of therapeutic (or preventative) options downstream that can specifically treat ever more specific sub-categories

Source: Scientia Analysis
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Healthcare business models and partnerships are evolving as a result of newfound applications of MDx technologies across the healthcare spectrum.

MOLECULAR DIAGNOSTICS IS FACILITATING PERSONALIZED MEDICINE FOR ALL STAKEHOLDERS

Source: Scientia Analysis
Changes to the drug discovery & clinical trial process is key to securing pharma’s future in personalized medicine

Personalized Medicine approaches impacts the pharmaceutical development process at almost every stage of a drugs lifespan

**Drug-Diagnostic Co-Development Opportunities**

*Personalized medicine approaches have the potential to de-risk development projects, shorten development timeframes, accelerate new product adoption, and generate additional revenue streams*

- Increased partnering & collaborative efforts to reduce risk
- Shorter timelines and cost for increased efficiency and broader portfolios
- Targeted clinical trials with smaller cohorts, potentially reducing cost and time
- Pricing based on smaller target population
- Consideration of the diagnostic into the process of drug pricing
- Pricing with clinical comparative effectiveness & health economic data

Source: Scientia Analysis
Several collaborations have recently been established where diagnostics are used to aid in the discovery process and identify disease-specific targets.

**NOTABLE ACTIVITY**

- **Genentech Partners with Xenon Pharmaceuticals in $646M Pain Pact (Jan 2012)**
  - Xenon’s strategic alliance with Genentech to discover and develop compounds and companion diagnostics for the potential treatment of pain
  - Xenon's discovery and development efforts focus on development of small-molecule therapies based on the genetic causes of metabolic, neurological, and cardiovascular disease

- **GlaskoSmithKline enters into companion program with diaDexus for heart disease drug**
  - LpPLA2 immunoassay, developed by diaDexus and approved for predicting the risk of heart disease and ischemic stroke
  - GlaxoSmithKline is developing a small molecule designed to inhibit this enzyme, thus reducing the risk of adverse cardiovascular events

Sources: Scientia Analysis; Company literature and press releases
Molecular diagnostics are also increasingly being used to refine patient populations for optimization of clinical studies …

Personalized Healthcare approach which includes collaboration of Diagnostics and Pharma as early as Phase II

**MetMab + Tarceva**
- Collaboration began in Phase II studies
- Roche cMET assay identified candidate metastatic NSCLC patients
- Trials showed that for patients with high Met, a combination use of MetMAB and Tarceva extended overall survival

Sources: Scientia Analysis; Company literature and press releases
...with additional collaborations occurring more frequently

- Abbott and Merck Collaborate to Develop Companion Diagnostic Test for Investigational Cancer Therapy (March 2012)
  - Collaboration to evaluate the use of a FISH-based companion diagnostic test to aid in the development of a Merck investigational cancer therapy
  - Abbott will develop a test to identify deletions of the TP53 gene in cancer patients and evaluated in clinical trials to help identify patients more likely to respond favorably to Merck's investigational cancer therapy

- Foundation Medicine, Novartis Ink New Deal for Clinical Oncology Programs (June 2012)
  - The use of Foundation Medicine's molecular information platform will be used across many of Novartis' Phase 1 and Phase 2 oncology clinical programs
  - Tumor genomic profiling has become an important part of Novartis' clinical trials

Sources: Scientia Analysis; Company literature and press releases
Several Rx/Dx approaches exist for targeted patient treatment

**Personalized medicine approaches are being used across all stages of the patient care cycle**
( oncology example shown)

1. Some women are at higher risk for breast cancer
2. Regular exams help detect lesions
3. If a cancer is found, it is staged by size and spread
4. Treatment based on the patient and her cancer
5. After treatment, cancer recurs in some patients
6. Some patients are being monitored

Sources: Scientia Analysis; Company literature and press releases

- DISCOVERY -
- LEAD OPTIMIZATION -
- PRECLINICAL DEVELOPMENT -
- CLINICAL DVPMT -
- FDA FILING, APPROVAL, LAUNCH -
- PATENT EXPIRY/GENERICS -

**DISCOVERY**
- Target Selection
- Target Validation

**LEAD OPTIMIZATION**
- Preclinical Characterization

**PRECLINICAL DEVELOPMENT**
- Patient Selection
- Clinical Trial Monitoring

**CLINICAL DVPMT**
- PH 1
- PH 2
- PH 3

**FDA FILING, APPROVAL, LAUNCH**

**PATENT EXPIRY/GENERICS**

**Physician Use**
Case studies of recently approved Rx/Dx exemplify how co-development can maximize value for the pharmaceutical companies.

**Value capture**
- **Therapy:** High
  - Vectibix® would not have had EU approval without KRAS data

**Co-development**
- Pfizer and Abbott collaborated for the simultaneous approval of Rx and Dx

**Value capture**
- **Therapy:** High
  - Vysis ALK Break Apart FISH Probe Kit: $1,500

**Therapy:** High
- Highly effective, orphan drug: $115,200 per year

**Sources:** Scientia Analysis; Company literature and press releases

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**Partnership Type**
- Amgen initially had a partnership with Dako to use pharmDx™ EGFR as a companion diagnostic

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**Partnership Type**
- Co-development: Pfizer and Abbott collaborated for the simultaneous approval of Rx and Dx
Several other partnerships are being established between pharma and diagnostic companies for companion diagnostics initiatives.

- **MDxHealth, Merck KGaA Partner to Develop Companion Dx for Glioblastoma Drug (July 2012)**

- **Eli Lilly collaborates with PrimeraDx for Companion Diagnostics Development (June 2012)**

- **Ventana to Collaborate with Bayer on Companion Diagnostic Test for new cancer biological cancer therapy (Jan 2012)**

- **Takeda and Zinfandel Pharmaceuticals Sign Licensing Agreement for Alzheimer’s Disease Biomarker in Combination with Pioglitazone (Jan 2011)**

Sources: Scientia Analysis; Company literature and press releases
Healthcare business models and partnerships are evolving as a result of newfound applications of MDx technologies across the healthcare spectrum.
As the average cost of sequencing declines, several opportunities emerge for life science tools companies to provide enabling technologies for personalized medicine.

### Key Pricing Trends

**Cost per Genome**

- **$5K today**
- **$1K Genome**
  - ~2012-2013

**Cost per MB**

- XGS Intro

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**AS COST OF SEQUENCING DECLINES…**

**...OPPORTUNITIES WILL EMERGE FOR LST COMPANIES**

### Technology

- Accuracy
- Read length
- Turnaround time

### Analysis and Expertise

- Proprietary analysis pipeline
- Specialized scientific staff
- Data handling

### Logistics

- Courier service
- Turnaround time
- Cloud-based access/delivery and tools

### Regulatory Standing and Expertise

- cGMP
- cGLP
- CLIA accreditation / ISO

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**Sources:**
- Scientia analysis; Wetterstrand KA. DNA Sequencing Costs: Data from the NHGRI Large-Scale Genome Sequencing Program
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For example, next-gen sequencers are increasingly being adopted for oncology MDx as price per base pair drops and throughput increases.

### Value Proposition of NGS in Oncology

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<th>RT-PCR</th>
<th>Sanger Seq’n</th>
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### Applications Suitability

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**In the near term, NGS is expected to move into areas of MDx that currently use Sanger sequencing, such as the analysis of K-Ras mutations. In the long term, NGS will be used in many areas where RT-PCR is currently being used.**

### Sequencing Players

- Life Technologies
- Illumina
- Helicos BioSciences Corporation
- Sequenom

### Key Takeaways

- Sales of next-gen sequencing (NGS) equipment are experiencing explosive growth with increasing use in MDx.
- IVD companies must assess the NGS opportunity and development strategy:
  - How attractive are clinical applications for next-gen sequencers market?
  - Whether to partner with NGS companies, or have their own NGS technology?
Post-2014, NGS/3GS technologies are likely predominate in oncology theranostics because of the need for higher predictive values.

In many situations a small number of markers will provide predictive values of less than 50%.

While this may represent a substantial improvement to the status quo upon introduction, competition amongst service providers drives demand for more comprehensive testing.

As the number of validated theranostic markers eclipses 100 (next 2-5 years), NGS/3GS platforms are expected to begin taking share.

Tests for the most common KRAS mutations (~10) will yield a negative predictive value of nearly ~50%

“The quality metrics have not been well established for the newer technology. That is ok in a research setting but can’t be tolerated in a clinical setting. As costs come down in the future, new technology could provide greater depth by running the same sample in multiple lanes.” – Oncologist, Weill Cornell Medical College
In addition to oncology, several other markets will be shifting towards greater use of sequencing technologies in the future.

**KEY TAKEAWAYS**

- As users needs for multiplexing and sensitivity becomes greater, there will be a transition to NGS/3GS technology.
- The shift within genetic testing is supported by competition among labs to provide the most comprehensive panels.
- The shift within sepsis and oncology prognosis have somewhat higher barriers to entry:
  - Sepsis requires < 6hr TaT and ease of use before considerable adoption
  - Oncology prognosis requires clinical trials, health economics and overcoming the early mover (GHDX)

**Note:** In the near term (2014) technology shifts to NGS/3GS are likely to see adoption rates similar to that of array comparative genomic hybridization (aCGH) for developmental delay observed over the past decade (~35% penetration a decade after introduction)

Sources: Scientia Analysis; ScientiaNET (KOL interviews)
As a result, Life Science Tools companies are expanding their capabilities and offerings in order to play a greater role in personalized medicine

Life Science Tools activity

NOTABLE ACTIVITY

• Life Technologies to follow Navigenics buy with more acquisitions as it builds MDx portfolio (July 2012)

• PerkinElmer to open new Personalized Medicine Center (June 2012)
  » The mission of the Center will be to create new enabling technologies for scientists developing and commercializing new diagnostic and therapeutic products

• GE Healthcare moves to develop lung cancer Dx (May 2012)
• GE to buy Personalized Medicine Company, SeqWright (April 2012)
• GE to Buy Clarient to Expand in Cancer Diagnostics (Oct 2010)

Sources: Scientia Analysis; Company literature and press releases
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Healthcare business models and partnerships are evolving as a result of newfound applications of MDx technologies across the healthcare spectrum.

MOLECULAR DIAGNOSTICS IS FACILITATING PERSONALIZED MEDICINE FOR ALL STAKEHOLDERS

Source: Scientia Analysis
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Payors are pushing for Rx-Dx integration; OncotypeDx has received increasing adoption and reimbursement since launch in 2004

**Payors reimburse Genomic Health’s OncoType Dx assay for breast cancer recurrence**

- Predicts likelihood of recurrence and benefit of chemotherapy for early stage (N- ER+) breast cancer
- Test based on algorithm and proprietary 21-gene panel using quantitative RT-PCR

**KEY TAKEAWAYS**

- Increasing adoption and reimbursement
  - Over 27,000 tests have been ordered by over 5,500 physicians since 2004
  - Approximately 80% of the population is covered for the test

**REFERENCES**

- Predicts likelihood of recurrence and benefit of chemotherapy for early stage (N- ER+) breast cancer
- Test based on algorithm and proprietary 21-gene panel using quantitative RT-PCR

**Economic Analysis of Targeting Chemotherapy Using a 21-Gene RT-PCR Assay in Lymph-Node-Negative, Estrogen-Receptor–Positive, Early-Stage Breast Cancer**

John Huestis Jr., MD; Leron E. Caruso, PhD, RN; and Gary H. Lynch, MD, MPH, FACP (Editor)

**RESULTS**

- For patients with lymph node-negative, estrogen-receptor (ER)-positive, early stage breast cancer 
- OncotypeDx provides information on treatment decision-making in patients with lymph node-negative, estrogen receptor-positive, early stage breast cancer 
- Payors reimburse Genomic Health’s OncotypeDx assay for breast cancer recurrence 

**CLINICAL**

- OncotypeDx provides information on treatment decision-making in patients with lymph node-negative, estrogen receptor-positive, early stage breast cancer 
- Payors reimburse Genomic Health’s OncotypeDx assay for breast cancer recurrence 

**Sources:** Scientia Analysis; Genomic Health company website

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Even PBMs like CVS Caremark is entering Personalized Medicine with promises of expanding PGx testing to improve patient health outcomes and cost

CVS Caremark, Generation Health to Expand PGx Testing to Millions
“CVS Caremark...has decided to expand pharmacogenomic testing...for certain drugs as of the second quarter of 2010” – GenomeWeb, Nov 10, 2009

Generation Health contracts PGXL to be preferred MDx lab “PGXL is a CLIA certified lab providing many PGx tests such as KRAS, CYP tests, Warfarin, Factor II, V & MTHFR and therapy monitoring tests.” - June 2010

KEY TAKEAWAYS

• Pharmacy Benefit Management companies like CVS Caremark are getting more involved in the personalized medicine revolution, looking to get establish themselves as a control point for information
  » In the past, Medco has run many studies to gather clinical data for PGx tests, such as KIF6 with Celera, in their “Genetics for Generics” program, as well as, launching their new TRC-AOS program to help educate and guide physicians regarding the right choices in testing, prescribing drugs, and monitoring for adverse events
  » CVS have developed relationships with sole service PGx test providers for access to lab testing capabilities

• Their move into personalized medicine will have a significant impact on drug prescription decisions, particularly to limit the use of branded drugs vs. generics

Sources: Scientia Analysis; Genomeweb
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Healthcare business models and partnerships are evolving as a result of newfound applications of MDx technologies across the healthcare spectrum.
Premier hospitals such as MGH are actively enforcing personalized medicine to enable better outcomes by taking knowledge management initiatives for data stored in EMRs and CDSS.

**IMPLICATIONS TO PERSONALIZED MEDICINE**

- This portal has revolutionary potential to translate the promise of personalized medicine into reality.
- The portal when expanded into an enterprise wide application across several labs/hospitals can be used to educate physicians, increase awareness of emerging high value MDx tests and accelerate adoption of these tests.
- IVD/MDx companies can use this portal to streamline their internal biomarker mining efforts to identify biomarkers with most clinical validity and utility for physician.

Sources: Scientia analysis, the Harvard Medical School Partners Healthcare Center for Genetics and Genomics

REF: NPC MDx and CDx Conference
Health IT companies are actively getting involved in PM by collaborating with payors to ensure accurate prescription of drugs.

Payors Adopt McKesson’s Automated InterQual Molecular Dx System to Avoid Inaccurate Coverage Decisions

- Pharmacogenomics Reporter – November 18, 2009

KEY TAKEAWAYS

• Although McKesson’s initial use of Molecular Dx in their InterQual CDSS is to manage the appropriate use of diagnostic testing, the likely next step will be to use diagnostic tests to guide therapeutic and prescription decisions and to manage coverage based on evidence.

• CDSS systems offered by health IT companies will have a significant impact on drug prescription decisions, particularly to limit the use of branded drugs vs. generics.

• McKesson's goal is to provide them with enough data and information to make informed decisions and not to tell health plans which of the ~2,000 MDx tests they should cover.

• In the US, health IT is gaining in importance as Obama’s healthcare reform mandates the implementation of electronic health records.

Sources: Scientia Analysis; Genomeweb
Press Release, July, 2011

McKesson Aims to Help Health Plans Navigate MDx, Genetic Testing Space “... McKesson is seeking to capitalize on the growing demand from health plans for help with MDx tests, and announced that 3 new health plans had joined its burgeoning list of clients using its products to help navigate the MDx space …” Press Release, July, 2011
Small and large health IT companies are also actively getting involved in PM by collaborating with providers to ensure accurate prescription of drugs

**Dana-Farber Informatics Team Launches GenoSpace to Link Genomic and Clinical Data via the Cloud**
“...GenoSpace, a Cambridge, Mass.-based informatics startup, has teamed with DFCI and launched a cloud-based platform intended to provide access to a variety of 'omic and phenotype data.” – Press Release, June, 2012

**DNA Nexsus Raises $15 Million, Teams With Google To Host Massive DNA Database**
“... raised funds from Google Ventures and TPG Biotech to help help scientists and genome-related services host and manage this data... announced a key partnership with Google to give long-term home to the Short/Sequence Read Archive (SRA) database which spans 400 terabytes at this point, includes publically available whole-genome sequences that scientists can use for research purposes....” – Press Release, Oct, 2010

**N-of-One Announces Agreement with Foundation Medicine to Provide the First Patient-Specific Genomic Diagnostic Solution for Precision Oncology**
“... provider of Diagnostic Strategy Roadmaps™ & Treatment Strategy Roadmaps™ for personalized cancer care, announced a strategic collaboration with Foundation Medicine, Inc. to support the development of its fully informative molecular cancer profiles that can be used to guide individualized patient treatment strategies...” – Press Release, May, 2012

**KEY TAKEAWAYS**
- Health IT companies are developing "roadmaps" to drive informed clinical decision-making by linking data about the molecular variations in each patient's cancer cells with leading-edge diagnostics, treatments, and technologies relevant to the tumor type
- In addition to providing a general data access portal, GenoSpace works with clients to build customized research portals to enable them to ask particular research questions
- Example - a user might want to locate candidates in a disease cohort that have a particular mutational profile required for a clinical trial
- Besides disease foundations, CROs, and pathology departments, other likely clients for GenoSpace and other such health IT vendors include pharmaceutical companies and information vendors

Sources: Scientia Analysis; Company literature and press releases
Such partnerships for genetic data collection, integration and analysis will enable PM CDSS rules that will remind physicians of a contraindications between drugs and certain mutations.

**EXAMPLE PM CLINICAL DECISION SUPPORT RULE**

*Partners Healthcare’s EHR contains a PM CDSS component which will remind a physician of a contraindication between TARCEVA and certain genetic mutations when the physician tries to prescribe this drug to a patient with the mutation.*

- **KEY TAKEAWAYS**
  - By reminding physicians of “easy to learn, easy to forget” information, CDSS tools can decrease variation in the use of various tests and interventions.
  - A CDSS will also be able to suggest options of published or guideline suggested therapeutic options allowing physicians to stay on top of the latest research and guideline changes.
Healthcare business models and partnerships are evolving as a result of newfound applications of MDx technologies across the healthcare spectrum.
Physician interest in personalized medicine is high but adoption of PM genetic testing will increase after physicians gain education and comfort with the tests

**NEED FOR PHYSICIAN EDUCATION**

- **United Healthcare survey** in 2012 reported that 75% of the physicians believe that there are patients in their practice who have not yet had a genetic test but would benefit from having one
- **Medco/American Medical Association survey** in 2009 reported that while 98% of physicians understand the value of PGx, they don’t feel they have the sufficient knowledge to comfortably order such tests

**UNITED HEALTHCARE: CENTER FOR HEALTH REFORM & MODERNIZATION SURVEY**

(US estimates 2012 - % Physicians)

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Genetic testing gives physicians the ability to dx conditions that would otherwise be unknown

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Genetic testing gives physicians the ability to dx conditions that could be prevented

**KEY TAKEAWAYS**

- In a Medco/AMA survey, almost all physicians indicated a lack of knowledge and comfort-level regarding personalized medicine tests currently available on the market today
- The education of physicians on correct use and applicability of the results of a PM test will greatly accelerate the adoption of that test
- Only ~400 out of 1300 molecular diagnostic tests have evidence based guidelines
  - To empower physicians, there is a need for a mechanism to move information from ‘bench’ to ‘point of care’
- There is increasing need for genetic counselors and cross-training of physicians in genomics and bioinformatics
- The Wideroff study published in 2003 found that test usage went up significantly when patients asked physicians about the tests

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Besides increasing physicians’ education and comfort, physician payment models may see modifications in order to promote MDx based approach to treating diseases

**EVOLUTION OF CANCER TREATMENT PARADIGM**

<table>
<thead>
<tr>
<th>Unlike the traditional approach ...</th>
<th>... MDx tools &amp; information enable ...</th>
<th>... a targeted approach in the future</th>
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<tr>
<td>• Type of cancer?</td>
<td>• Type of cancer?</td>
<td>• Predisposition/Prognostic Dx/Rx?</td>
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<td>• Genetic variation?</td>
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<td>• Theranostic Dx/Rx?</td>
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<td>• Genetic resistance to therapy?</td>
<td>• Monitoring Dx/Rx?</td>
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Examples: Newly proposed physician payment models being evaluated include ....

- **OPTION A:** Treating oncologist can choose the least expensive clinical pathway approach OR choose an alternative if patient displays drug resistance
  - Oncologists rewarded for compliance with the clinical pathway through higher fee schedules, bonus programs, or other forms of incentives

- **OPTION B:** a "bundled payment" or an "episode payment," reimburses medical oncologists upfront for an entire cancer treatment program vs. using the current "fee-for-service" approach that rewards volume regardless of health outcomes
  - Payment based on the expected cost of a standard treatment regimen for the specific condition, as predetermined by the oncologists

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UnitedHealthcare Report Recommends Adopting New Cancer Care Payment Model to Reward Physicians for Health Outcomes

*Health Affairs article examines current cancer care payment system and alternative strategies to reduce costs and improve health outcomes for patients*

MINNETONKA, Minn. (April 16, 2012) – A new report from UnitedHealthcare examines the current cancer care payment system and considers alternative strategies to reduce costs and improve health outcomes for patients.

According to Dr. Newcomer, ‘Paying physicians for a total treatment cycle promotes better care and eliminates the incentive to prescribe costly drugs that may not be the most effective treatment option.’

Sources: Scientia analysis; United Healthcare Working paper
As a result, providers like Dana-Farber and Brigham & Women's Hospital join to launch PROFILE for genetic research, one of the most extensive national level research projects in cancer genomics yet.

Dana-Farber, Brigham and Women's launch PROFILE, a large-scale research program to scan tumors for mutations, establish extensive genomic database (Oct 2011)

- **Goal of PROFILE**
  - To leverage access to patients’ tumor samples and genetic testing tools to scan tumor tissue for hundreds of gene mutations linked to cancer

- **Advantages of PROFILE**
  - Enable clinicians to treat more cancers with mutation-specific targeted therapies in the future
  - Expand with the discovery of additional cancer-related mutations
  - Develop more advanced screening technologies
  - Patient eligibility for clinical trials

Sources: Scientia Analysis; DFCI
37 | Scientia Advisors | July 24, 2012 | REF: NPC MDx and CDx Conference
Healthcare business models and partnerships are evolving as a result of newfound applications of MDx technologies across the healthcare spectrum.
As treatment becomes more personalized, patients believe they will have more options and view personalized medicine as a tool to improve healthcare.
Patients are already becoming exposed to the possibilities of personalized medicine…

In Treatment for Leukemia, Glimpses of the Future

ST. LOUIS — Genetics researchers at Washington University, one of the world’s leading centers for work on the human genome, were devastated. Dr. Lukas Wartman, a young, talented and beloved colleague, had the very cancer he had devoted his career to studying. He was deteriorating fast. No known treatment could save him. And no one, to their knowledge, had ever investigated the complete genetic makeup of a cancer like his.

Sources: Scientia Analysis; Industry news; Company literature and press releases
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… however, until regulations are standardized, patients will experience the impact of personalized medicine primarily through approved channels

Providing a DTC genetic test off-the-shelf ...

... received a negative reaction from the FDA

Walgreens postpones plans to sell personal genetic tests

May 12, 2010 | By Madison Park, CNN

Walgreens has postponed its plans to sell personal genetic test kits after the Food and Drug Administration intervened. Genetic kits from Pathway Genetics, a nationwide drug store chain, started generating controversy and public interest in the approved genetic test market. After the agency contacted the company, the kits are no longer on the sale.

Sources: Scientia Analysis; Company literature and press releases

41 | Scientia Advisors | July 24, 2012 | REF: NPC MDx and CDx Conference
Agenda

• The Role of MDx in Personalized Medicine
  » Recent Industry Trends
  » Evolution of Business Models

• Public Policy Considerations

• Future Directions
Government agencies are increasing their attention towards cost effectiveness and patient outcome measures that include the use of molecular or genetic tests

GOVERNMENT INTEREST IN PERSONALIZED MEDICINE

Several U.S. federal agencies are involved in personalized medicine

US Health Reform legislation includes the establishment of the Patient-Centered Outcomes Institute (PCOI)

• Comparative Effectiveness Research (CER) will include primary research
• Will take into account individual and subpopulation differences, including genetic and molecular subtypes
• Experts appointed will include those in genomics and CER
...but proposed funding of $10-150 MM is inadequate

The UK is increasing attention to in vitro diagnostic tests

“New NICE programme to evaluate medical technologies established” – NICE, Nov 16, 2009

KEY TAKEAWAYS

• The US has funded outcomes research via several agencies. Current legislation, if enacted, may establish an explicit agency responsible for effectiveness research, although effective funding is not yet clear.
• European Health Technology Assessment (HTA) agencies, such as the UK’s NICE and Germany’s IQWiG, have traditionally focused their outcomes and cost-effectiveness research on pharmaceuticals. They are now turning their attention to diagnostics and devices. Diagnostics that control drug costs are obvious winners.

Sources: Rugnetta and Kramer, “Paving the Way for Personalized Medicine”; Scientia research; press releases; BIVDA;
Scientia Advisors | July 24, 2012 | REF: NPC MDx and CDx Conference
The FDA has been accelerating their involvement in development of molecular diagnostics and pharmaceuticals to enable personalized medicine.

**PM DIAGNOSTICS ACTIVITY**

**First PGx Test Approved**
*Dec. 24 2004:* The FDA approved AmpliChip CYP450 test, the first FDA approved PGx test.

**FDA Approves Agendia’s Mammaprint**
*Feb. 6 2007:* The FDA approved Agendia’s MammaPrint Dx for breast cancer recurrence, the first IVDMA test.

**FDA Simultaneously Approves Roche/Plexxikon's Drug, Companion Dx for BRAF-Mutated Melanoma**
*Aug. 17 2011:* The FDA approved Roche's personalized melanoma drug Zelboraf alongside a companion genetic test.

**FDA Clears Qiagen KRAS Test as CDx for Erbitux**
*July 2012:* FDA cleared marketing of therascreen KRAS RGQ PCR Kit to be sold as a companion diagnostic test for Erbitux (cetuximab).

**PM PHARMACEUTICAL ACTIVITY**

**FDA Withheld Approval of Zarnestra**
*May 2005:* Zarnestra was not approved by the FDA for AML because Johnson & Johnson did not have evidence in their trial that the drug was more effective than chemo. FDA’s Oncologic Drug Advisory Committee on Zarnestra believed that the trials would have more effective if a diagnostic was utilized to determine patients that were not eligible for chemotherapy.

**FDA Updates Plavix Label**
*May 2009:* The FDA updated Plavix label with pharmacogenetic data informing doctors and patients of diminished response to the drug and increased risk of heart attack in patients with reduced CYP2C19 function.

**FDA Updates Vectibix and Erbitux Labels**
*July 2009:* The FDA updated the “indication and usage” section of Amgen’s Vectibix and BMS/ImClone’s Erbitux to include “retrospective analyses of metastatic colorectal cancer trials have shown not shown a treatment benefit for the EGFR inhibitors in patients whose tumors had KRAS mutations in codon 12 or 13," and that the use of the drugs is not recommended for the treatment of CRC patients with these mutations.

Sources: Scientia Analysis; GenomeWeb
For example, the FDA released a guidance with recommendations on how to label RUO tests for their intended purposes …

OVERVIEW OF FDA RUO GUIDANCE DOCUMENT

FDA recently released a guidance document* reminding manufacturers of the requirements applicable to RUO and IUO IVDs. The aim is to control the clinical diagnostic use of IVDs in order to prevent the possibility of misinformed clinical decisions that may ultimately lead to adverse patient health consequences. The document is not legally enforceable; however, they represent current recommendations and suggestions on labeling and marketing these tests by the FDA.

GUIDANCE ON RUO/IUO LABELING

• Appropriate RUO labeling refers to IVD use strictly for research intended to evaluate the test itself or in non-clinical laboratory research. These tests are inappropriate for use in diagnostic procedures.

• Appropriate IUO labeling refers to the use of IVDs in an investigation, but it is not to be used for clinical diagnosis without confirmation from another established product or procedure.

GUIDANCE ON RUO/IUO MARKETING

• Advertising, promotion, support or sales of RUO IVD for use in clinical investigation, clinical diagnostic use, or for LDT development meant for clinical diagnosis conflicts with the intended use of an IVD labeled RUO.

• Advertising, promotion, support, or sales of IUO IVD for use in non-investigational diagnosis, or use that is inconsistent with an exempt investigation conflicts with the intended use of an IVD labeled IUO.

Notes: RUO- Research Use Only; IUO – Investigational Use Only; *Draft guidance released on June 1st, 2011 titled “Draft Guidance for Industry and FDA Staff - Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions.”
On June 16, 2010, the U.S. Food and Drug Administration (FDA) announced its intention to dramatically expand its regulatory oversight of laboratory-developed tests (LDTs)

For years, the FDA had adopted a policy of “enforcement discretion” in declining to closely regulate LDTs. However, an expanding and changing LDT marketplace, along with heightened government and media scrutiny of certain LDTs, including high-complexity tests and tests marketed directly to consumers (DTC), has caused the FDA to reconsider its policy of enforcement discretion. FDA’s has ongoing attempts and inititaites to develop a comprehensive system of oversight for LDTs

• FDA issued 4 Letters to Knome, 23andMe, deCODE Genetics, and Navigenics requesting that their full genome testing service be submitted for FDA approval
• A similar letter sent to Pathway Genomics, coinciding with announcements of Walgreens’ intent to stock the firm’s Insight Saliva Collection Kit for genetic testing
• Illumina, who supplies 23andMe and deCode with the array for the genome test, was sent a letter taking issue with the RUO status of the array
Overall, government interests globally are increasing towards the incorporation of molecular or genetic profile information for improved patient care.

**GOVERNMENT INTEREST IN PERSONALIZED MEDICINE**

Several U.S. federal agencies are involved in personalized medicine

Patient Protection and Affordable Care Act (Obamacare)

- Includes provisions for allowing FDA approval for biologic drugs, increasing Medicaid drug rebate for brand name drugs, supporting comparative effectiveness research

NICE OKs AstraZeneca Iressa For Lung Cancer After Cost Deal

May 26, 2010 – NICE recommends the use of AstraZeneca drug Iressa for NSCLC patients after AstraZeneca offers the product to patients for free if treatment is less than 3 months. The drug was previously rejected for its cost efficiency and effectiveness.

Italy Health Ministry pushes for greater use of low cost generics

June 2010 – New package seeks to balance incentives to stimulate research with the need to lower overall drug bills

**KEY TAKEAWAYS**

- President Obama’s Patient Protection and Affordable Care Act, nicknamed Obamacare, will upon enactment authorized generic biologic FDA approvals, increase Medicaid drug rebate for brand names, and support comparative effectiveness research

- European Health Technology Assessment (HTA) agencies such as the UK’s NICE and Germany’s IQWiG have traditionally focused their outcomes and cost-effectiveness research on pharmaceuticals

  » In Iressa’s case, NICE recommended use of the drug for NSCLC only after AstraZeneca agreed to provide the drug to patients for free if use was below 3 months

- HTAs are now also turning their attention to diagnostics and devices. Diagnostics that control drug costs are obvious winners.

- Health Ministries in Europe including Italy, Germany and the Netherlands are also pushing for increased use generic drugs over branded to lower cost

Sources: Rugnetta and Kramer, “Paving the Way for Personalized Medicine”; Scientia research; press releases; BIVDA

47 | Scientia Advisors | July 24, 2012 | REF: NPC MDx and CDx Conference
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In summary, it is imperative for stakeholders to focus on innovative business models to capitalize on molecular diagnostics and its evolving role in healthcare thus, improving patient care cost-effectively.

**NEW APPROACH TO DURG DISCOVERY, DEVELOPMENT & COMMERCIALIZATION FOR OPTIMAL PATIENT CARE**

**Shift in healthcare driven by MDx technologies and patient information**

**PAST**
- Broad therapies (1 drug per disease population e.g., hypertension)
- Trial & Error; large scale comprehensive screenings
- Model focused on physicians only

**FUTURE**
- Targeted therapies for a patient subgroup (e.g., Selzentry for CCR5 HIV, - Trofile®)
- Biomarkers, genetic variation, pathways, patient outcome
- Model focused on all major stakeholders

**GENERAL OVERALL APPROACH**
- R&D
- COMMERCIAL

**Source:** Scientia Analysis
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Molecular diagnostics are driving personalized medicine, but the path to market is still filled with many hurdles

**Biomarker Development Issues**
- Discovery and validation of biomarkers can be expensive and who owns the IP?
- Technological hurdles of assay development
- Hurdles associated with manufacturing personalized therapies

**Coverage and Reimbursement Issues**
- Which tests specifically will save costs?
- The need for long-term results data
- Use of out-dated analysis models that do not factor in small, niche populations addressed by personalized medicine
- Price sustainability issues – how high will personalized medicine costs go?

**Business Model Considerations**
- Big pharma’s commitment to biomarker investment
- How will the diagnostic be marketed as a kit or certified CLIA lab as is currently being done
- Regulatory hurdles as most assays are now central lab CLIA based
- Which assay platform should be used as that affects pricing and marketing
- Joint ventures vs partnerships due to the different goals of Rx and Dx companies
Key questions and strategic options for pharma companies

**KEY QUESTIONS**

- **Regional Regulatory Differences**
  » What exactly will EU and Asian countries require from a CDx?

- **Regulatory Interactions**
  » What is the appropriate time for regulatory submissions and interactions?

- **Non-Pivotal Prospective Trials**
  » For a non-pivotal study (e.g., Phase 2 or 1b), what are the regulatory requirements for patient stratification (e.g., neuregulin study)?

- **Co-Development Timelines**
  » What are the co-development timelines for each potential CDx / drug program?
  » Is it possible to proceed into a phase 3 trial without full analytical validation?

- **Commercial Model**
  » What are the business model options?

- **Pricing and Reimbursement**
  » What is the pricing and reimbursement landscape for companion diagnostics?

- **IP**
  » What is the value of the IP? What is the key IP to have?

- **Diagnostic Vendors**
  » Who are the potential diagnostic partners for each test / modality?

**STRATEGIC OPTIONS**

1. **PARTNER TO DEVELOP CDX UNDER PMA PATHWAY**

2. **USE CE-MARKED ROUTE**

3. **LEVERAGE PARALLEL LABELS**

4. **OTHERS?**
Mapping Out Strategic Options (High-Level)

### Personalized Medicine Strategy Selection Framework

<table>
<thead>
<tr>
<th>Quadrant</th>
<th>Details</th>
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<tbody>
<tr>
<td>1</td>
<td>Close Partnership with Dx Co.</td>
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<tr>
<td></td>
<td>• DxCo has no incentive to commercialize</td>
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<tr>
<td></td>
<td>• Pharma has interest in test commercialization</td>
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<tr>
<td></td>
<td>• PharmaCo must subsidize commercialization</td>
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<tr>
<td>2</td>
<td>Arms Length Relationship</td>
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<tr>
<td></td>
<td>• DxCo has incentive to commercialize</td>
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<td></td>
<td>• PharmaCo also has interest in test</td>
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<td></td>
<td>• Deal is optional and may further increase NPV of Dx and Therapeutic</td>
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<tr>
<td>3</td>
<td>Defensive Maneuvers</td>
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<tr>
<td></td>
<td>• DxCo has incentive to commercialize</td>
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<td></td>
<td>• Pharma has incentive to limit uptake</td>
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<td></td>
<td>• Pharma should carefully assess risk mitigation ideas</td>
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<tr>
<td>4</td>
<td>Monitor potential PBM relationships</td>
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<tr>
<td></td>
<td>• DxCo has no incentive to commercialize</td>
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<td></td>
<td>• PBM has incentive to contain Rx cost</td>
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<td></td>
<td>• Pharma should consider the impact of potential Dx/PBM deals</td>
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Source: Scientia Advisors